moderate altitude. Tucson, Arizona, Phoenix, Arizona, and Yuma are comparatively low. The accompanying table of elevation, soil and latitude is appended for reference. I quote from the editorial in *American Medicine,* November, 1907, soon after the publication, in the *New York Dietetic and Hygienic Gazette,* of my article on this same subject:

> And what can be said of Dr. Clarence L. Wheaton of Chicago, who says that the ideal climate would be the one possessing the greatest possible amount of sunshine when he should know that for a third of a century there has been obtained the best results in the world in the Adirondacks, which are noted for the absence of sunshine, and if he really exposes his patients to what is now known to be harmful to them, we commend his cases to the trustees of that institution.

We have here evidence of commendable loyalty to the home climate, but it is seemingly unwise to attribute "the best results" in the world to a given health resort; the physician endeavoring to substantiate such a claim would meet with tremendous opposition from all quarters. As for sunlight or even sun heat being harmful to tuberculous patients when properly utilized, the facts herewith presented speak for themselves, no contributions to the literature covering this subject, either by climatologists or phthisiotherapists, have been presented, so far as I am aware, denying the effects here attributed to the sun's influence. The government has established at great expense in Colorado and New Mexico sanatoria for the treatment of tuberculous soldiers and sailors. These respective climatic zones approach our ideal in the choice of a climate, and the untoward effects of sunlight have not as yet been reported.

To one enlisted in the antituberculosis crusade in a great city like Chicago the study of climatology is of interest and value from a scientific standpoint alone; the rôle it plays here in the solution of the tuberculosis problem is an insignificant one.

The chain of dispensaries established by the Chicago Tuberculosis Institute and their affiliation with regularly organized relief and aid societies will eventually solve the medical and sociologic problem as it is presented to the worker here. The state sanatorium will in time be constructed and enable us properly to utilize the home climate in arresting tuberculosis. The results of the sanatorium treatment in so-called unfavorable climates has far exceeded our expectations. Let us be frank to admit that some climates are better than others; that they possess certain attributes exerting a decided beneficial influence in pulmonary disease; but with all our knowledge of these facts we must know that most of those afflicted should avail themselves of the home environment, for the end of the bow of promise for the average traveling consumptive rests on the mystic shores of the spirit land.

My long residence in Colorado and study of climatic conditions throughout the southwest have convinced me that often without regard to the circumstances of the patient or stage of his disease, it has been the custom to prescribe change of climate. Nothing can be more cruel or irrational than this; in the case of those too poor to afford the expense incident to a change, it opens the door to regrets which are likely to harass the mind when it most requires repose. In most instances the disease progresses more rapidly to a fatal termination, and in many cases the expatriated invalid finds not only a foreign climate but a foreign grave.

There are hundreds of human wrecks scattered over the desert waste of the great southwest, and thousands wandering in the mountain wilderness of some distant state, struggling for the mere necessities of life, with death an inexorable companion, and all the future dimmed by the shadow of waiting Charon.

Our knowledge of these facts must impress on us all the responsibility we assume in prescribing change of climate, yet let us recognize the fact that in selected cases climate is not all fallacy, and that it plays its rôle in the hygiene of tuberculosis.

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THE CONJUNCTIVAL TUBERCULIN REACTION AS A MEANS OF DIAGNOSIS AND CONTROL *

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It should be plainly stated and clearly understood that tuberculin tests of whatever nature are but confirmatory evidence for the substantiation of clinical findings. A large proportion of cases of pulmonary tuberculosis are capable of being diagnosed by the practitioner from examination of the local focus and consideration of the clinical history. In these cases fever, emaciation, cough with sputum more or less characteristic, and consolidation or destruction of lung tissue are sufficient evidence. These cases, however, form the long list of incurables, and diagnosis has its main importance in so far as it affects prophylaxis. It is in incipient or early involvements that the greatest amount of effort should be exerted toward diagnosis, because these patients are to a large extent curable, and cure means the ridding a community of a class of persons inimical to public health and public economy. These incipient cases of tuberculosis frequently present many elements of doubt as to diagnosis even after the most thorough physical scrutiny. If they are not tuberculous it is a great injustice to ostracise them; if they are tuberculous it is beneficial both to the patients themselves and their fellows that they be treated as such. It is in this class of patients particularly that diagnostic tuberculin tests are warranted. The choice of test to be applied depends on a variety of circumstances and conditions.

It will be granted that whatever tuberculin test is used must be convenient, rapid in execution and manifestation, inexpensive, harmless and dependable before it can be recommended for general use for the examination of one or of many hundred patients. By convenient we must understand tests which are readily submitted to and easily and accurately followed. The rapidity of execution and manifestation of the reaction are points of weighty moment when many people are to be tested in a comparatively short time or when the patient happens to be the support of a family or the manager of a business. In the examination of school children, candidates for life insurance, for the army or the navy, in the routine inspection of factories or lodging-houses, etc., where the expense is borne by municipalities or by private individuals, the cost of material for the tuberculin test is frequently a prime cause of its not being used. All tuberculin tests must be harmless to the great majority, else this fact will doubtless be strongly urged against their use by unwilling subjects, imperfectly trained physicians or misinformed officials. As a consequence, both prophylaxis and cure will be interfered with. Inasmuch as tuberculin tests are to be taken as confirmatory evidence—evidence which is frequently final and crucial—then it goes without saying that such tests must be dependable

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The conjunctival tuberculin test, as directed to be practiced by Calmette and others, is admittedly the most convenient, rapid and inexpensive means of administering tuberculin for diagnostic purposes. It is impossible to conceive of a maneuver more simple than the instillation of a drop of a non-irritating solution into the conjunctival sac and then in the main merely watching for the appearance of evidences of conjunctivitis in the instilled eye. The rapidity of execution and manifestation of positive reactions make this method ideal when large numbers of patients are to be tested and when time and assistance are limited. The chief objections that have been urged against its employment are that it is not altogether harmless and that there is question as to its dependability. It is with these questions that we shall principally concern ourselves.

A. CONSIDERATION OF THE SAFETY OF THE CONJUNCTIVAL TEST

Harmlessness of Tuberculin Tests in General.—The application of any tuberculin test is essentially the introduction into an organism of a substance which is foreign to it. This foreign substance is in effect a poison, whether it be introduced by the subcutaneous, the cutaneous, the inunction, the rhinologic, the pharyngeal or the conjunctival routes. The manifestation of the body's defensive powers constitutes the tuberculin reaction, modified for the form of application of the test. It may be stated, then, that improperly controlled, whether as regards, amount, time, class of patient or method of application, all tuberculin tests are capable of producing harmful results. This was early shown by Virchow[1] and others respecting the subcutaneous injection of Koch's "old tuberculin," and more recently by Trudeau and Baldwin[2] and Thelling[3] for the Koch's "new tuberculin." Pick[4] has lately mentioned the finding of fragments of tubercle bacilli in preparations of "old tuberculin *Hochst*," used in the cutaneous reaction of v. Pirquet, and has found that the lesions produced as a result of positive manifestation of the reaction are in many ways similar to tubercles in parts of the body actively infected with the tubercle bacillus. In respect to the conjunctival reaction, attention has been frequently called to inconveniences and actual disability of the ocular apparatus which may follow indiscriminate instillations.

The harmful results from the use of the conjunctival test have mainly followed (a) when tuberculin was instilled into eyes which were not altogether normal, (b) when the patients were not kept under observation but were allowed to become exposed to dirt, mechanical irritants and infection, or (c) when unsuitable preparations of tuberculin were used. Calmette[5, 6] reports 1,000 personal observations and 13,000 instillations performed by workers other than himself, and states that in no case in which the tests were properly applied and controlled were there serious complications. Petit[7] tabulated 2,974 instillations with no ill effects out of 698 positive reactions. Mantoux[8] mentions no eye injury from instillation of 200 children. Ausset,[9] commenting on 300 tests also in children, speaks of but one case in which the positive reaction was the cause of any considerable inconvenience. In this child there was a prolonged conjunctivitis following the instillation. He believes that rubbing the eye and secondary infection were responsible for the condition. Etienne[10] tabulates no harmful consequences following the instillation in about 100 old men. In the routine examination of soldiers Simonin[11] records one case of kerato-conjunctivitis which he is inclined to consider as evidence of secondary infection. Citron[12] reports no unfavorable results from instillation in 115 cases in which the instillations had been carefully made and the patients watched. In 54 typhoid patients who were instilled with tuberculin, out of 20 positive reactions Cohn[12] noted no harmful consequences. Fritz-Levy,[13] after 300 instillations, considers the procedure safe when properly carried out. Lignieres[14] observed no ill effects following 200 instillations in cattle. Denis[15] calls attention to the fact that there were no harmful results in his cases even when the subjects were febrile. Levy[16] speaks of no eye complications in 120 instillations. Blum[17] instilled 240 patients, all ages, tuberculous and non-tuberculous, without harmful results. Schroeder and Kaufmann,[18] after 125 instillations, claim that when the eyes are examined before the instillation there is no danger of harmful results. Damask[19] instilled 74 patients, with no injurious effects; Morelli[20] tabulates 276 cases, tuberculous and non-tuberculous, but reports no permanent inconvenience to the eyes. In 220 cases Levi[21] cites two severe reactions: one in an old case of carcinoma with cachexia and the other in a patient with old tuberculous cervical glands. The latter patient had rubbed his eyes. Wolff,[22] from 101 observations, mentions two cases in which severe conjunctivitis followed, but fails to make mention of the eye examinations preceding the instillations. Stadelmann[23] reports no severe reactions following instillations in eyes which were negative before instillation. Of 100 cases Gaupp[24] noted no severe reactions. Of 310 instillations in tuberculous and non-tuberculous patients Cohn[25] mentions no serious ocular disturbances. In our own experience,[26] working with 1 per cent. solutions in normal salt solution, of more than 450 instillations in 377 individuals we have observed but four prolonged or stubborn reactions. These were: a case of splenomyelogenous leuke-

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1. McFarland: Pathogenic Bacteria, 1906, p. 335.
2. Med. News, Aug. 28, 1907.
3. Centralbl. f. Bakteriol., July 5, 1902, p. 28.
4. Pick: Semaine médicale, Jan. 29, 1908, p. 59.
5. Calmette: Semaine méd., Jan. 22, 1908, p. 46.
6. Progrès méd., Feb. 22, 1908, p. 97.
7. Petit (quoted by Ausset): Rev. de méd., April 10, 1908.
8. Mantoux: Rev. de la Tuberc., February, 1908.
9. Ausset: Rev. de méd., April 10, 1908.
10. Etienne: Rev. méd. de l'est, April 1, 1908.
11. Simonin: Semaine méd., No. 48, 1907, p. 575.
12. Citron: Deutsch. med. Wchnschr., 1908, No. 8, p. 316.
13. Fritz-Levy: Deutsch. med. Wchnschr., 1908. No. 3, p. 194.
14. Lignières: Semaine méd., Dec. 4, 1907, p. 586.
15. Denis: Soc. clin. d. hôp. de Bruxelles, Province med., July 13, 1907.
16. Semaine méd., Feb. 12, 1908, p. 84.
17. Blum: München. med. Wchnschr., Jan. 14, 1908, p. 60.
18. Schroeder and Kaufmann: München. med. Wchnschr., Jan. 14, 1908, p. 62.
19. Damask: Wien. klin. Wchnschr., 1908, No. 4, p. 121.
20. Morelli: Wien. klin. Wchnschr., 1908, No. 3, p. 83.
21. Levi: Berl. klin. Wchnschr., Feb. 3, 1908, p. 261.
22. Wolff: Berl. klin. Wchnschr., 1908, No. 6, p. 295.
23. Stadelmann: Deutsch. med. Wchnschr., 1908, No. 7, p. 271.
24. Gaupp: Deutsch. med. Wchnschr., 1908, No. 7, p. 275.
25. Cohn: Berl. klin. Wchnschr., Nov. 25, 1907. p. 1507.
26. Smithies and Walker: THE JOURNAL A. M. A., Jan. 25, 1908, l, 259 and herewith.

mia, with old, postoperative cervical glands, leukemic retinitis and iritis with many adhesions; one case of old syphilitic keratitis, with history of early involvement of the cervical glands (before the patient contracted lues); one case of chronic Bright's disease associated with a high degree of arteriosclerosis, marked sclerotic fundus changes and increased intraocular tension; one case of long-standing arthritis deformans with apical tuberculous involvement, who responded to the conjunctival test after a subcutaneous injection of 1 mg. T. A.

Unfavorable evidence against the conjunctival reactions is scant when one eliminates that associated with cases in which patients presented eye changes before reaction came on. It is possible to conceive how in the course of instillation of many eyes even superficial lesions may be overlooked. It is certain that the way the conjunctival test is practiced in many large hospitals and dispensaries, in this and other countries, there is abundant opportunity for such lesions as iritis, keratitis, corneal ulcer, ocular tuberculosis and affections of the vitreous and fundus to escape notice.

After instillation, when people are allowed to go about their ordinary duties with the eyes unprotected, it is not unlikely that positive reactions can be aggravated and prolonged by mechanical irritants. In both children and adults rubbing the eyes has been shown to influence the severity and the duration of the reaction (Ausset,[9] Citron,[12] Calmette,[6] Wolff-Eisner[27, 28, 29] Levi,[21] the authors[26] and others). In hospitals, barracks, schools or neighborhoods where contagious ophthalmias are prevalent a positive conjunctival test may readily furnish a point of least resistance for the beginning of a specific infectious process, as suggested by Citron.[12] Variations in strength and character of tuberculin instilled appear to be responsible for a certain proportion of severe positive reactions and possibly for reaction in people not tuberculous. Solutions of old tuberculin varying in strength from 1 to 10 per cent. have been used, and of the precipitated, dried residue in solution, strengths of from 0.1 to 4 per cent. have been suggested. Preservatives, as glycerin and carbolic acid, have been variously added. One rarely finds mention of whether human, bovine or mixed cultures have been used. The solvents have been either normal salt solution or sterile, distilled water. Frequently the strength of solution has not been varied between children and adults; often many instillations have been made into the same eye at short intervals; the stage of the disease has received little study from most writers. It is not to be wondered at that unlooked-for consequences have sometimes followed.

A few writers have noted general harmful effects, as distinct from local eye changes. Occasionally severe facial neuralgia and headaches have been reported (Demarest and Arloing[30] and authors[26]). Febrile changes have been observed in a few instances (Demarest and Arloing,[30] Wolff,[22] Treupel[31] and others). In no case, however, were the general symptoms so marked as in a characteristic subcutaneous tuberculin reaction.

B. CONSIDERATION OF THE DEPENDABILITY OF THE CONJUNCTIVAL REACTION

1. *Necessity for Proper Technic.*—We have before[26] called attention to the mistakes which may follow careless instillation or the failure to make sure that the tuberculin instilled is not washed out by tears, wiped out or washed out intentionally after the physician has left. We have not thought best to instill into the inner canthus, as suggested by certain French and German writers (Calmette,[32] Wolff-Eisner[27] and others), but have preferred to hold the lower lid away from the eyeball, and while the patient's head is tilted back and eyeball turned upward we instill the drop into the inferior cul-de-sac. The lid is gently moved over the eyeball a few times, the lids are approximated for a few moments, the patient being directed to rotate the eyeball several times. Both before and after instillation all parts of both conjunctivæ, caruncles and semilunar folds are compared while the eyeballs are rotated in all directions. Abnormalities are noted in writing. Examination after instillation should be made frequently after the third hour.

2. *Consideration of Preparation.*—Our former work was done with 1 per cent. solution (?) of tuberculin prepared according to the formula of Calmette. Our results were in accord with those published by the majority of French writers. The preparation used was demonstrated to contain fragments of bacilli. The tuberculin was said by the manufacturers to be made from virulent, human and bovine cultures of the tubercle bacillus grown on 5 per cent. glycerin bouillon. Inasmuch as later it appeared desirable to the manufacturers to put forth a product absolutely free from tubercle bacilli, a process of extra purification was introduced. With the ordinary microscope this could not be said to contain any fragmented cells. It is not impossible, however, that they may have been revealed by the ultra-microscope, as suggested by Pick.[4] This second lot of tuberculin, which was supplied us in tablet form, was not dependable. The reactions were poorly manifested and the percentage of positive reactions was considerably lower for all classes of tuberculosis than had been given by our early preparation. We were able to establish this fact by comparative tests, fortunately having preserved some of the first samples submitted to us. Our results agreed in the main with those of other clinics where the second lot of tuberculin had been used in comparison with the first. The reason for this discrepancy involves considerable detail. Suffice it to say that, as shown by Detre[33] and T. Smith[34] too much precipitation and heating with hot alcohol, and the use of bovine tubercle bacillus cultures, or material derived from a mixture of bovine and human tubercle bacilli, might reasonably be expected to account for some of the differences noted. A proper preparation should be entirely from human tubercle bacillus growths, from virulent cultures grown on a proper medium. In the consideration of statistics from various sources it is absolutely essential that one know with what preparation the tests were made. The tendency in Germany appears to use solutions of from 0.25 to 4 per cent. "old tuberculin *Höchst*." The French observers mainly follow the originally marketed preparation of dried, precipitated tuberculin in from 1 to 2 per cent. strength. Distilled water or physiologic salt solution are used as solvents. It has been clearly pointed out by many observers, notably Schmidt,[35] Citron,[12] and Damask,[19] that severe

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[27] Wolff-Eisner: Berl. klin. Wchnschr., 1907, No. 22.

[28] Wolff-Eisner: Beitr. z. klin. d. Tuberk., 1908, lx, 1-189.

[29] Stadelmann and Wolff-Eisner: Deutsch. med. Wchnschr., 1908, No. 5, p. 181.

[30] Province méd. Oct. 12, 1907.

[31] Treupel: München. med Wchnschr., Jan. 14, 1908, p. 66.

[32] Calmette: Rev. internat. de la Tuberc., xiii, No. 2, 1898, p. 119.

[33] Detre: Wien. klin. Wchnschr., Feb. 6, 1908, p. 173.

[34] Smith: Jour. Exper. Med., 1898, p. 451.

[35] Schmidt: München. med. Wchnschr., Jan. 14, 1908, p. 66. (Breslau cases.)

conjunctival reactions may be brought on by the use of 1 per cent. dried "tuberculin *Hochst*," whether glycerin mixed or free, and that 0.1 per cent. strength is sufficient to bring about results corresponding to the preparation of 1 per cent. strength sent out from the Pasteur Institute at Lille. It has been well shown also by Damask[19] that the Pasteur Institute preparation is at least two and one-half times as effective as is the 1 per cent. solution of "old tuberculin *Hochst*." It thus appears that when possible tuberculin prepared according to Calmette's originally described method is the most reliable. The variations in the results stated with the use of other preparations may also have been influenced by the variation in virulence of the growths from which the tuberculin was derived, the use of bovine cultures in the attempt to bring about reaction in humans, the use of bacilli grown on improper media, and the classes of cases in which each of the various forms of tuberculin was used. It will be readily understood how difficult it is to review statistics of reported work when such work has been done under so great a variety of conditions. It seems proper to compare separately the results from German and from French clinics.

3. *Results in Cases Known to Be Tuberculous.*—A summary of 1,554 cases of tuberculosis, all stages, from the reports of German observers (Fritz-Levy,[13] Daus,[36] Levy,[16] Blum,[17] Cohn,[25] Morelli[20] and Gaupp[24] reveals positive conjunctival response in 86 per cent.

Of more than 14,800 French cases tabulated from the writings of Mantaux,[8] Petit,[7] Ausset,[9] Comby,[37] Calmette[38, 6] and others, positive evidence was given in 93 per cent.

In our own experience 15 cases of incipient pulmonary tuberculosis were all positive, of 20 cases of bone tuberculosis 80 per cent. were positive. In 74 cases of moderately advanced pulmonary tuberculosis positive manifestations were secured in 75.6 per cent., with slight ocular changes in an additional 13 per cent. Of 42 cases of pulmonary tuberculosis, including moribund and miliary tuberculosis, positive reactions were secured in 59.5 per cent., with suspicious eye changes in an additional 15 per cent. In summary, of 151 cases of known tuberculosis, all stages, positive manifestations were secured in more than 79 per cent. In incipient and early cases positive manifestations were secured in 93 per cent.

4. *Presence of Reaction in Doubtful Cases.*—Of 476 cases in which tuberculosis was suspected, German statistics (Blum,[17] Schroeder and Stadelmann,[29] Morelli,[20] Levi,[21] Wolff[22] and Gaupp[24]) exhibit positive reactions in about 51 per cent.

With French writers the proportions are rather higher. Of 273 cases (Ausset,[9] Petit,[7] Grasset and Rimbaud,[39] Dufour[40]) 64.5 per cent. showed positive ocular manifestations. In Calmette's résumé of 14,000 cases he states that 61 per cent. of patients suspected of having tuberculosis gave distinct reactions.

In our own series, of 13 suspected tuberculous patients positive conjunctival changes were noted in 9, or in 69 per cent. It is possible that we secured a higher percentage of reactions than German or French writers because we were able to keep our cases under observation constantly from the time of instillation. Perhaps, however, were our series larger we should approach proportions similar to those of other workers.

5. *Presence of Reaction in People Apparently Well.*—Of 1,379 cases not clinically tuberculosis in the writings of German workers (Fritz-Levy,[13] Blum,[17] Schroeder and Kauffmann,[18] Morelli,[20] Levi,[21] and Cohn[21]) there were 9.9 per cent. positive conjunctival tests.

In Calmette's summary 18 per cent. of those not suspected of having tuberculosis gave positive manifestations. He suggests that this is in proportion to the gross percentage of tuberculous lesions found at autopsy. In Petit's[7] summary of 938 patients, many of whom were children, about the same percentage was obtained. He calls attention to the fact that many of his patients had adenoids and enlarged tonsils. Etienne,[10] working with old men, was able to secure positive conjunctival manifestations in 66 per cent., which he mentions is about the same proportion as Bruardell claims tuberculous lesions are found in the aged at autopsy.

Our own work shows that of 205 cases not clinically diagnosed as tuberculous 13 revealed positive ocular changes. This percentage, 6.8 per cent., is lower than that noted by other writers. Explanation might be found in the fact that many of our hospital patients were anemic, some were tested with poor tuberculin, and there were many young adults. Of 76 instillations in young men apparently well, but two gave positive ocular manifestations. In both of these there were fairly well marked signs of tuberculosis.

6. *Presence of Positive Conjunctival Reactions in Diseases Other than Clinical Tuberculosis.*—Much proof has been advanced to show that the conjunctival reactions are not specific for tuberculosis. The same sort of proof has long been held against all forms of tuberculin test, particularly the subcutaneous. It has long been maintained that patients affected with syphilis, leprosy and actinomycosis respond to the subcutaneous injections. Probably the same might have been noted had tuberculin been used subcutaneously in various acute infectious diseases, as typhoid fever, scarlet fever, articular rheumatism, etc. The contraindication to the use of the tuberculin may have been responsible for the lack of positive evidence. We have not been able to discover work in which negative evidence has been furnished. It has been urged by many that in typhoid fever, particularly, conjunctival tuberculin reactions may be obtained. The excellent work of Kraus, Lusenberger and Russ,[41] and the reports of Cohn[25] and Blum,[17] seem to furnish evidence that the occurrence of the reaction is not altogether accidental. The reaction appears to be most constant in convalescents. It is not always obtained, as shown in Levy's[15] cases. In one of Montagnon's[42] typhoid cases, in which the patient died, abundant evidences of tuberculosis were discovered. In our own series we failed to get positive evidence after two instillations in a case of typhoid in a young adult. A case of miliary tuberculosis suspected of being typhoid for some days gave positive conjunctival reaction after injection subcutaneously of 1 mg. of TA. Fortunately for clinicians and public health officers, incipient tuberculosis is rarely mistaken for typhoid. When the two exist together, then again one must emphasize the fact that all tuberculin tests are but confirmatory evidence. Several writers (Citron[12] and Blum[17]) call attention to

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36. Daus (quoted by Fritz-Levy): Deutsch. med. Wchnschr., 1908, No. 3, p. 194.
37. Comby: Semaine méd. July 31, 1907, p. 271.
38. Calmette: Progrès méd., Jan. 25, 1908, p. 45.
39. Province méd., July 13, 1907.
40. Dufour: Societe Méd. hôpitaux, Semaine med., July 24, 1907, p. 358.
41. Kraus, Lusenberger and Russ: Wien klin. Wchnschr., 1907, No. 45, p. 1385.
42. Montagnon: Presse méd., July 20, 1907.

the fact that positive conjunctival reactions may be obtained in syphilitics and cases of acute articular rheumatism. Citron[12] suggests that the reaction may be due to old lesions that make themselves manifest as a result of the secondary change. Blum[17] has noted the reaction in nine cases of scarlatina, in eight cases of lobar pneumonia and in six of sepsis. He does not furnish evidence to show that in these cases it was possible to exclude tuberculosis, typhoid, syphilis or previous eye lesions.

The experiments of Arloing[43] have been frequently cited as indicating the non-specificity of the conjunctival test. In brief, they consisted in injecting subcutaneously into rabbits, supposedly non-tuberculous, successive doses of tuberculin, diphtheria toxin, typhotoxin and staphylotoxin. The eye reaction in all cases was found negative before the injections. After the eighth daily dose of toxins eye changes were noted in all classes of animals, particularly in those which had been injected with typhotoxin and tuberculin. The serum reactions of each remained negative during the entire list of tests. At postmortem no evidences of tuberculosis were discoverable in any of the animals. Criticism of this work might be freely offered. There were no control rabbits. The rabbits were not protected after instillation; reactions were not noted until after the eighth dose of subcutaneous toxin, or about at the tenth day, a proper period of sensitization. There were no rabbits injected at the same time with tuberculin subcutaneously, with note as to whether or not they developed fever reaction. A series of four rabbits is too small a number from which one may draw conclusions. Finally, clinically, there should be no difficulty in distinguishing between tuberculosis, typhoid fever, diphtheria or sepsis. De Lapersonne[44] calls attention to the fact that reaction similar to the conjunctival test may be produced after intoxication with abrine and serpent venom. Inasmuch as these occurrences are infrequent, the observation can have little practical value, although it has considerable scientific interest.

7. *Presence of Positive Conjunctival Reaction in Cases in Which Tuberculin Has Been Used Subcutaneously, Either for Diagnostic or Therapeutic Effect.*—This is a factor that has doubtless led to much confusion. If, after patients have received two subcutaneous injections of tuberculin, according to the method of Koch, at an interval of several days, without reaction, and then positive reaction is manifested when tuberculin is instilled on the conjunctiva, discredit is likely to be thrown on the method. The work of many writers (Dumarest and Arloing,[30] Baldwin,[45] Hutchins,[46] Fritz-Levy,[13] Cohn[25] Damask,[19] Stadelmann and Wolff-Eisner,[29] the authors[26] and others) demonstrate that in patients who have received two or more cutaneous injections for curative or diagnostic purposes conjunctival reactions may be produced, may be brought out after being negative, may be aggravated if already present, or may become again evident weeks after they have subsided. The patients who have been the longest under treatment with subcutaneous injections show a lower percentage of response, with frequently less pronounced reaction, than do those in whom there have been few, fairly large doses of tuberculin, subcutaneously (as when tuberculin is used diagnostically in ascending doses). Patients under treatment with tuberculin may, however, fail to react, as shown by Baldwin[45] and Schroeder and Kaufmann.[18] Cases of incipient tuberculosis show more prompt and vigorous responses than do middle or late stage cases (Damask[19]). Patients with tuberculosis frequently show violent reaction after subcutaneous injections when the tuberculin has been instilled in the same eye. Patients not tuberculous may exhibit conjunctival reaction after several injections of small doses of tuberculin subcutaneously (Cohn[25] and authors[26]). This is particularly so when the subcutaneous injections are continued at intervals after the tenth day. There is less response when the subcutaneous injections are small, as TR for therapeutic effect, than when the dose is fairly large, as TA for diagnosis.

8. *Comparison of Results Obtained with Conjunctival Tuberculin Tests and Various Other Tests.*—As yet there is little literature available on the inunction, the rhino-tuberculin[47] and the pharyngeal-tuberculin[48] tests, so they may be left out of consideration. Statistics compiled from many sources seem to point to the fact that, for greatest accuracy when the test can be carried out on hospital or sanitarium patients, the subcutaneous test is somewhat more reliable than cutaneous or conjunctival tests. Unfortunately, however, concerning the subcutaneous method statistics are usually quoted in regard to its diagnosis only of early or incipient cases, which are fever-free, whereas statistics are quoted for conjunctival and cutaneous tests from whole number of patients tested, be they incipient, moderately advanced or moribund cases. The subcutaneous method, for obvious reasons, has been little tried on apparently healthy persons. When it has, results have been not altogether favorable. (Franz obtained positive reactions in 61 per cent. of "able-bodied recruits" to the Bohemian army.) One can not conceive that all these were syphilitics, lepers, actinomycotics, trypsin or peptone poisoned individuals!

When the conjunctival, the cutaneous and the subcutaneous tests are compared as regards incipient or early stage cases, the percentages of positive reactions do not greatly vary, and, after all, this is the stage when tuberculin should be used. Calmette's statistics on 14,000[38] cases give the percentage of positive reactions with the conjunctival, early cases as 92 per cent. Schroeder and Kaufman[28] in 971 cases of tuberculosis as 88.5 per cent. In our own series the conjunctival reaction was positive in 93 per cent. of early and moderately advanced cases. It is difficult to get actual figures on the subcutaneous method. In but very few clinics, however, are percentages over 90 exceeded.[33, 34] It is not quite proven that repeated injections of tuberculin for diagnostic purposes are not capable of ultimately producing reaction in cases which are not tuberculous or where the lesions are very old and inactive. Especially does this seem so where from six to ten injections are made during a few weeks. The securing of reaction in incipient cases by the repeated injection of the same size dose, as shown by Hinman and Wolman,[49] is very significant. Doubtless hypersensitization may be thus produced quite as distinctly as with the conjunctival method. In respect to the relative merits of the cutaneous (v. Pirquet's) and the conjunctival tests, numerous comparisons are available.

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[43] Arloing: Prov. méd., Feb. 1, 1908, p. 54.

[44] De Lapersonne: Presse méd., Dec. 7, 1907.

[45] Baldwin: THE JOURNAL A. M. A., Dec. 14, 1908, xlix, p. 1969.

[46] Hutchins: Therap. Gaz., Dec. 15, 1907.

[47] Lafite, Dupont and Molinier: Jour. de méd. de Bordeaux, Feb. 16, 1908.

[48] Plehn: Deutsch. med. Wchnschr., 1908, No. 8, p. 315.

[49] Johns Hopkins Hosp. Bull., Aug. 1, 1907.

In 114 cases of tuberculosis, Morelli[20] obtained positive cutaneous reaction in 98 per cent. and positive eye changes in 86 per cent. He neglects to state which test was applied first. It is possible that the one exerted a perceptible sensitizing effect on the other. In cases of suspected tuberculosis, the v. Pirquet reaction was positive in 94 per cent., the conjunctival in 47 per cent. In 96 cases not clinically tuberculous, the cutaneous reaction was positive in 21 per cent. of the cases, the conjunctival in 11 per cent. The latter figure agrees rather closely with that obtained by other workers. There is a question as to whether or not secondary infection does not increase the percentage of positive reactions, so-called, to the v. Pirquet reaction. This appears to be particularly likely when dispensary patients are treated and then allowed to depart with the skin improperly protected. Several of Morelli's cases showed at autopsy old tuberculous processes when both conjunctival and cutaneous reactions had been negative. Wolff's[22] figures are slightly in favor of the skin test, especially for children. He has noted radiograph indications of infiltration when the cutaneous reaction was negative. Stadelmann[23] cites a case in which the cutaneous reaction was positive and the subcutaneous negative until injection of 5 mg. TA. He is inclined to think that the conjunctival test is valuable in early and suspected active cases, while better results may be obtained with the cutaneous test in quiescent lesions. He calls attention to the prognostic value of both reactions. Usually they both appear with severity in inverse ratio to the virulence of the infection. This severity is in direct proportion to the patient's protective powers. The instillation, application or the injection of tuberculin derived from bovine tubercle cultures might affect the results with the various tests, as suggested by Detre.[33] Wolff[22] states that in his experience the cutaneous and the conjunctival tests have shown very similar results. Other statistics might be cited.

In general, then, it may be stated that when properly applied and controlled the conjunctival tuberculin test shows results which compare favorably with those obtained by the subcutaneous and cutaneous methods. The facility with which this test may be applied and wider range of its usefulness speak strongly in its favor. It has been suggested that the subcutaneous injection might be used to supplement the conjunctival test (Citron,[12] Vallée,[50] Schroeder and Kaufmann,[18] Stadelmann,[23] Fritz-Levy[13] and others).

9. *The Question of Interpretation of Positive and Negative Results.*—This question is one which deserves attention. It appears that when the conjunctival reaction is prompt (typhoid, mechanical irritants in the eye, or irritant properties in the tuberculin instilled being excluded, and with the use of a suitable preparation in so far as strength, character of bacilli, etc., are concerned) there is good reason to consider that the patient is tuberculous. The test in these cases will doubtless be readily confirmed by local or general examination. A negative reaction in a suspected individual should not be taken to mean that the case is non-tuberculous. In doubtful reactions, cytologic examination for polynuclear leucocytes in the eye discharge may be made, as suggested by Lafite, Dupont and Molinier.[47] It is best, however, to make a second instillation after two days' interval in the eye not previously instilled. It is sometimes advisable to use stronger solutions at this instillation. (Eppenstein,[51] Fritz-Levy[13] and others). If this second instillation is negative after two or three days one may safely say that the patient is free from active tuberculous lesion. Reinstillation later into the first eye might be possible with the same strength solution as first used, but after five days there is strong probability that the second instillation may produce local hypersensitization and reaction in people not actively tuberculous, or a very severe reaction in cases tuberculous. In more than 100 instillations in moderately severe and moribund cases, we have never seen a case fail to respond to a second instillation of 1 per cent. solution in the same eye, when such instillation were made within three days. We have frequently noted that people not tuberculous clinically failed to show ocular changes, when from three to five instillations were made in the same eye within ten days. We have also reported instances[26] in which after the tenth and as late as the twentieth day repeated instillation of 1 per cent. freshly made solution failed to produce conjunctival changes in persons not clinically tuberculous. In moribund cases we have had negative reactions to one instillation made in eyes which had been instilled a month previously, but positive manifestations to second instillation made two days later in the same eye. We have also noted response to the second instillation made in the previously non-instilled eye.

The local anaphylaxis in tuberculous individuals may persist for weeks and even months. This has already been commented upon in the literature. We have noted a case in which conjunctival changes appeared spontaneously three times in an eye where rather severe reaction had followed the second instillation (made within four days). The case was one of old tuberculous hip-joint disease. During five months following the first instillations the patient had three attacks of night pains, tendernesss over the hip joint, with disability. Each time conjunctival changes appeared and lasted for from one to three days. The first spontaneous reaction was the most pronounced. These facts are significant. Patients should always be questioned regarding whether or not they have previously submitted to the conjunctival test, and if so, with what result. We have never seen, either in the literature or our own experience, a case in which prolonged sensitization was maintained in patients free from tuberculous taint.

In our work we have made an attempt to correlate the instillation time with respect to the clinical symptoms, especially with regard to the instillation in patients febrile and not febrile. In a few instances of early and moderately advanced pulmonary tuberculosis with fever, we have secured prompt and vigorous responses to the first instillation. But we have also noted reactions equally prompt and equally vigorous in patients who were afebrile. We have never, however, failed to secure prompt and well-pronounced response in febrile tuberculous patients, whereas in many cases of tuberculosis which were afebrile we have secured delayed and not well-marked conjunctival changes. This fact suggests that in incipient or early cases of pulmonary involvement better results could be expected from instillations made in the afternoon, when such patients are apt to have rises in temperature. The point requires more confirmation however.

It would appear from the foregoing discussion of the work of others and ourselves that the questions of the harmlessness and the dependability of the conjunctival reaction to tuberculin were fairly well supported, and that as a method whereby confirmation of more or less extensive physical examinations is desired it has numerous advantages over other forms of tuberculin test. In the rapid examination of large numbers of cases, as for example, in the army and navy, public institutions, schools, manufacturing establishments, immigrants, etc., the method appears to be of great worth. It should be preceded or supplemented by local examination in all instances before final judgment can be given. It may be combined satisfactorily with the subcutaneous method when deemed necessary as the weight of evidence appears to be that these reactions reinforce each other.

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[50] Vallée: Progrès méd., Feb. 8, 1908, p. 69.

[51] Eppenstein: München. med. Klin., Sept. 8, 1907.

In the routine examination of many individuals it appears desirable that a general scheme of work be followed out, that the best results may be obtained.

First: Accurate register of each patient tested should be kept in convenient form. A chart enables us to watch each patient thoroughly and furnishes a valuable lot of information for the subsequent study of cases and the reaction. On this chart is recorded the patient's name, age, sex, preparation of tuberculin used, eye in which it is instilled, date and time of instillation, reaction, including time beginning, degree and time ending, and whether slight, moderate, pronounced or very pronounced.

Second: A proper preparation must be insisted on. In all instances it should be freshly made—with sterile diluents — physiologic salt solution or water. That manufactured according to the original method of Calmette appears most desirable. It is conveniently marketed in 1 per cent. solution and in powdered form. We have always preferred to use sterile, physiologic salt solution as a diluent, and have found the 1 per cent. solution satisfactory. It might be advisable in picked cases, *e. g.*, children and febrile patients, to use the 0.5 per cent. solution. If preparations of "old tuberculin" are used, then solutions of various strengths might be prepared according to the method of Eppenstein[51] (1, 2 and 3 per cent.) or of Fritz-Levy[13] (0.5, 2 and 4 per cent.).

In children, and particularly in scrofulous patients, even weaker solutions than 0.5 per cent. may be used with satisfactory results. If a preparation of the "dried tuberculin *Hochst*" be used then 0.1 per cent. solution is amply strong. If stronger are employed severe and prolonged reaction, with perhaps serious damage to the eye may follow.

Third: Examination of the eyes for evidence of old or recent lesions.

Fourth: After instillation, the eye should be protected from rubbing, mechanical irritants, injury and secondary infection. This may be managed in adults by giving them simple directions; in children celluloid shields or eye-pads may be adjusted. Violent reactions can be appropriately treated by cold applications, mildly antiseptic eye washes, or washes containing astringents.

Fifth: Reinstillations should be made in the eye not first instilled, and if the preparation is from old tuberculin, the strength of the solution should be increased in order to obtain the best results. If instillations are made in the eye first instilled, then positive evidence is not possible after the fifth day. If instillations are made in the other eye positive evidence is doubtful after the tenth day.

CONCLUSIONS.

In the routine examination of many individuals tuberculosis is readily overlooked unless some form of tuberculin test is administered. These tests, however, are but confirmatory of physical findings.

The conjunctival tuberculin test as directed to be practiced by Calmette and others is convenient, rapid in application and manifestation, inexpensive, can be used in febrile cases, is practically harmless when properly carried out and controlled, and is, in the hands of the general practitioner, for incipient and early cases, as dependable as are any other forms of tuberculin test.

Proper technic, proper preparation, discrimination in the interpretation of both positive and negative reactions, and care of the patients following instillation are necessary for the success of the reaction.

Patients presenting disease of the eye other than simple conjunctivitis should not be instilled.

Second instillations should be made in the opposite eye. Positive reaction in this is dubious after the tenth day, if the suspected focus is not examined.

Care should be taken to eliminate recent typhoid, colon infections, syphilis and acute infections, as diphtheria, sepsis, scarlet fever and articular rheumatism. Patients receiving tuberculin subcutaneously for diagnostic or therapeutic purposes may be expected to react, frequently irrespective of active tuberculous foci.

Prompt, positive manifestation generally means an active focus with good systemic resistence. This is especially so in early cases. Delayed response, with feeble ocular changes, may be considered as of bad prognostic import in both early and late stages of the disease.

Severe conjunctival disturbances may result from reinstillation in the same eye, particularly in tuberculous individuals, and after the tenth day in others. Sensitization of the conjunctiva may persist for months and reinstillation may be responsible for violent reaction. This may be aggravated by synchronous or subsequent subcutaneous use of tuberculin.

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BIBLIOGRAPHY

In addition to the authorities cited in the text, the following may be consulted:

Beck: Deutsch. med. Wchnschr., 1899, p. 137 .
Butler: Brit. Med. Jour., April 18, 1908.
Calmette: Compt. rend. de l'Acad. d. sc., 1907, vii, No. 29, 1907; Presse médicale, June 1908; Gaz. hebd. d. sc. méd. de Bordeaux, Aug. 4, 1907.
Comby: Progrès méd., July 27, 1907, p. 470.
Delorme: Gaz. d. hôp., Feb. 13, 1908, p. 210; Prov. méd., Feb. 1, 1908. Notes de clinique, p. 54.
Downes: Brit. Med. Jour., Dec. 7, 1907.
Eyre, Wedd and Hertz: Lancet, London, Dec. 21, 1907.
Fraenkel, A.: Pathologie der Lungenkrankheiten, Berlin, 1904, p. 843.
Lautier: Semaine méd., Feb. 5, 1908, p. 64; Gaz. hebd. d. sc. méd. de Bordeaux, Dec. 22, 1907.
Lemoine: Rev. de la Tuberc., February, 1908.
MacLennan: Brit. Med. Jour., Dec. 7, 1907.
Moeller: Semaine méd., Feb. 12, 1908, p. 84.
Montagnon: Province méd., Jan. 18, 1908, p. 27.
Noeggerath: Semaine méd., Jan. 29, 1908, p. 59.
Ricketts: Immunity and Serum Therapy, 1906.
Simon and Spillman: Rev. méd. de l'est., Feb. 1, 1908.
Statineanu: Ref. d. Biochem. Zentralbl., 1907, p. 811.
Stephenson: Ophthalmoscope, Dec. 1, 1907.
Webster and Kilpatrick: Brit. Med. Jour., Dec. 7, 1907.
Wiens and Gunter: München. med. Wchnschr., Jan. 28, 1908, p. 180.
Wolff: Semaine méd., Jan. 29, 1908, p. 60.
Wolff-Eisner: München med. Wchnschr., Jan. 14, 1906, p. 65.